UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,646	08/21/2000	Yasuko Ozaki	053466/0286	8792

22428 7590 02/18/2010
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
02/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/622,646	OZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _14 October 2009_.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1-4 and 6-17_ is/are pending in the application.

4a) Of the above claim(s) _3,4,10-12 and 14-16_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1,2,6-9,13 and 17_ is/are rejected.

7)☒ Claim(s) _1 and 17_ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _21 August 2000 and 19 September 2008_ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment filed 10/14/2009 is acknowledged and has been entered. Claims 1, 7-9, and 17 were amended. Accordingly, claims 1-4 and 6-17 are pending in the application with claims 3-4, 10-12, and 14-16 currently withdrawn. Claims 1-2, 6-9, 13, and 17 are subject to examination below in light of the elected species of *a protein having the amino acid sequence modified by lacking **17** amino acid residues from the C-terminal of SEQ ID NO:20.*

Objections/ Rejections Withdrawn

2. The objection to the specification regarding sequence compliance is withdrawn in response to Applicant's arguments (Reply, pages 11-13) and in view of the instant amendments to the specification.

3. The objections to claims 1, 7-8 and 17 have been withdrawn in response to Applicant's amendments to the claims.

4. The rejections under § 112, first paragraph have been withdrawn in response to Applicant's amendments to the claims.

5. The rejections under § 112, second paragraph have been withdrawn in response to Applicant's amendments to the claims and in view of Applicant's arguments on the record regarding the meaning of the term "**soluble**" as it applies to the claimed invention (Reply, pages 14-15). In particular, Applicant has clarified that the term "soluble" refers to the fact that the protein is <u>not bound to a cell membrane</u> (rather than referring to the ability of the protein to dissolve in a solute).

6. The rejections under § 102(b) as being anticipated by Goto et al. have been withdrawn in response to Applicant's amendments to claims 1 and 17 to recite a protein "consisting of" (rather than "having") the indicated amino acid sequence(s).

7. The rejections of claims 1-2, 6-7, 13, and 17 under § 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al., Gastinel et al., and Lauffer et al.; and of claims 8-9 as being unpatentable over these references and further in view of Frank et al., have been withdrawn in response to Applicant's amendments to claims 1 and 17 to recite a protein "consisting of" (rather than "having") the indicated amino acid sequence(s).

Priority

8. The present application was filed on 8/21/00 and is a national stage (371) entry of PCT/JP99/00885, filed 2/25/99. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 10-60613, filed on 2/25/98 in Japan.

Claim Objections

9. Claims 1 and 17 are objected to because of the following informalities:

10. In claims 1 and 17, lines 2-3, it is suggested that the phrase "reacting soluble HM1.24 antigen protein **and** anti-HM1.24 antibody contained in a test sample" be changed to --reacting soluble HM1.24 antigen protein <u>with</u> anti-HM1.24 antibody contained in a test sample-- for clarity.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-2, 6-7, 13, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 555, 560-577, and 591-592) in view of Ishikawa et al. ("Molecular cloning and chromosomal mapping of a bone marrow stromal cell surface gene, BST2, that may be involved in pre-B-cell growth" Genomics. 1995 Apr 10;26(3):527-34), Gastinel et al. (U.S. 5,623,053), Lauffer et al. (U.S. 5,639,597), Laping et al. (U.S. 5,866,693), and Lo et al. (U.S. 5,541,087).

Harlow & Lane teach antibody-capture assays, in which an antigen is bound to a solid phase in order to capture specific antibody present within a test sample (see page 555, Figure 14.1 in particular; and pages 560 and 562-577). Such assays are useful, for example, in

quantitating antibodies and can be used to compare the epitopes recognized by different antibodies (see especially at page 563, first paragraph).

Harlow & Lane therefore teach immunochemical assays of the same format as claimed instantly, in which an antigen is bound to a solid support and used to detect antibodies specific to the antigen in a test sample. However, Harlow & Lane fail to teach soluble HM1.24 antigen protein as the type of antigen, and similarly fail to teach anti-HM1.24 antibodies as the type of antibodies detected.

Ishikawa et al. teach the antigen BST-2, which is a human membrane protein expressed on bone marrow stromal cells (the abstract). It is noted that BST-2 as taught by Ishikawa et al. is the same protein referred to in the instant specification as HM1.24 antigen. This is evident by referring to the predicted amino acid sequence for the 180-residue BST-2 protein in Figure 4 of Ishikawa et al., which is the same sequence disclosed instantly as SEQ ID NO:16 (the full-length human HM1.24 antigen). The authors conducted functional studies which suggested that this antigen may be involved in stimulating pre-B-cell growth (abstract; page 528, left column, first paragraph; page 531, right column, first sentence; and page 532, right column, last paragraph).

When taken together with the teachings of Harlow & Lane, therefore, it would have been obvious to one of ordinary skill in the art to pursue immunochemical antibody-capture assays using the novel BST-2/HM1.24 antigen taught by Ishikawa et al. as the type of antigen in order to detect antibodies specific to BST-2/HM1.24 in a test sample according to the methods of Harlow & Lane. One would be motivated to do this in order to quantify such antibodies and/or to compare their epitopes as part of experiments to further study a newly discovered protein of importance in pre-B-cell growth.

However, Ishikawa et al. further teach that the BST-2/HM1.24 protein is a transmembrane protein (the abstract).

Those of skill in the art at the time of the invention recognized certain technical considerations for dealing with antigens that are transmembrane proteins.

For example, Gastinel et al., in discussing the transmembrane FcRn receptor, teach that the hydrophobic nature of the receptor's transmembrane domain precludes the solubilization of the protein in aqueous buffer without the use of surfactants, which are often toxic, difficult to remove, and can reduce the stability of proteins (column 4, lines 43-50). As a result, the usefulness of the membrane-bound receptor is limited by the fact that, like other transmembrane proteins, is not readily soluble in aqueous solutions without surfactants (column 4, line 66 to column 5, line 2). By contrast, Gastinel et al. teach that there are many applications for an Fc receptor that is soluble in aqueous solutions without the use of a surfactant (column 4, lines 51-65; column 11, lines 62-67). Gastinel et al. further teach that such soluble receptors can be produced by removal of the transmembrane domain (column 5, lines 3-20; column 6, lines 1-10; column 10, lines 48-57). In addition, the soluble receptors of Gastinel et al. maintained the ability to bind to antibodies and can be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

Lauffer et al. discuss how binding experiments involving transmembrane receptor proteins can be carried out while the receptors remain bound to the cell, but that such assays are increasingly difficult as the number of receptors in the cell membrane decreases (column 1, lines 8-35). To avoid this drawback, Lauffer et al. propose receptor binding assays using soluble fusion proteins in place of membrane-bound receptors, in which the extracellular domains of

human membrane proteins are fused to the constant part (Fc) of the heavy chain of an Ig (column 1, line 35 to column 2, line 40). Such fusion proteins retain their biological activity (column 1, lines 62-67). The fusion proteins can be produced as secreted proteins in animal cells and easily purified by affinity chromatography via their Fc part, e.g. on a sepharose matrix (column 2, lines 4-18).

Similarly, Laping et al. teach Fc fusion proteins in which proteins or parts thereof are fused to the immunoglobulin constant or Fc region (column 9, line 55 to column 10, line 27). Laping et al. also contemplate fusion proteins involving membrane-bound receptors, in which one or more of the extracellular domain, the transmembrane domain, or the cytoplasmic domain of the receptors are used as components of the fusion protein (column 10, line 28-36).

Laping et al. further teach that for some uses, it is desirable to be able to delete the Fc part after the fusion protein has been expressed and purified (ibid; as well as the abstract and claims 9-12). This is the case when the Fc portion proves to be a hindrance, for example, when the fusion protein is to be used as an antigen. This is done by linking the two components of the fusion protein with a cleavable linking region, e.g. a cleavage sequence that can be cleaved with factor Xa.

Lo et al. also teach fusion protein expression systems that enhance the production of a given target protein, in which an encoded target protein is fused to a secretion cassette such as an Fc domain, which allows for purification by binding to protein A. See column 1, lines 5-20; column 2, line 62 to column 2, line 56; and column 4, lines 46-60.

Lo et al. also contemplate production of essentially any target protein using this system, including target proteins that are normally non-secreted proteins. For example, if a desired target

protein includes sequences encoding a secretion signal or a transmembrane signal, these sequences can be removed so that the fusion protein is secreted as a soluble protein (column 8, lines 1-21; column 1, lines 16-20). Thus, by using this Fc fusion system, a higher level of protein expression may be obtained (see also column 13, lines 50-55).

Lo et al. further teach that a proteolytic cleavage site is interposed between the encoded target protein and the Fc region, allowing it to be cleaved (ibid and column 5, lines 8-24; column 3, line 66 to column 4, line 2).

The teachings of Gastinel et al., Lauffer et al., Laping et al., and Lo et al. indicate that those of skill in the art recognized certain technical obstacles that may arise when working with transmembrane proteins. In addition, these references indicate that in order avoid such obstacles, it was known to use soluble forms of such transmembrane proteins (for example, soluble receptor-Fc fusion proteins) in place of the full-length, membrane-bound proteins.

In this regard, it is noted that in addition to identifying BST-2/HM1.24 as a transmembrane protein, Ishikawa et al. (discussed above) also constructed a soluble form of BST-2/HM1.24, in which the putative extracellular region of was fused to the Fc region of human IgG1 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4).

When taken together with the teachings of Gastinel et al., Lauffer et al., Laping et al., and Lo et al. therefore, it would have been obvious to one of ordinary skill in the art to employ a soluble form of the BST-2/HM1.24 antigen when performing antibody-capture assays for anti-HM1.24 antibodies according to the method of Harlow & Lane and Ishikawa et al. More

particularly, it would have been obvious to employ BST-2/HM1.24 antigen in which the transmembrane domain had been removed. One would be motivated to use a soluble form instead of the full-length antigen because to avoid potential technical problems known to arise when using full-length transmembrane receptors. For example, it would have been obvious to remove the transmembrane domain and express the extracellular domain of the BST-2/HM1.24 antigen as a fusion protein with Fc as done by Ishikawa et al., in order to enhance production of the antigen using this known Fc fusion protein system (as also taught by Lauffer et al., Laping et al., and Lo et al.).

With respect to the limitation that the soluble HM1.24 antigen protein used in the method is one “consisting the amino acid sequence modified by lacking the last 17 amino acid residues from a C-terminus in the amino acid sequence of SEQ ID NO:20”, Ichikawa et al. illustrate a soluble BST-2/HM1.24 antigen fused to Fc as discussed above. This fusion protein therefore does not *consist* of the indicated amino acid sequence, since it contains the Fc region in addition to amino acids of BST-2/HM1.24.

However, in light of the teachings of Laping et al. and Lo et al. as discussed in detail above, it would have been obvious to one of ordinary skill in the art to first produce the soluble BST-2/HM1.24 as an Fc fusion protein and then to subsequently cleave off the Fc region. In particular, these references indicate that it was known in the art to exploit Fc fusion proteins to express and purify soluble proteins, and also that it was known to subsequently remove the Fc tag. As such, it would have been obvious to prepare soluble BST-2/HM1.24 as a fusion protein with Fc (as illustrated by Ishikawa et al.) and then to subsequently cleave off the Fc region, via use of a cleavable linker as taught by Laping et al. and Lo et al. One would be motivated to do

this since as recognized by Laping et al., it can be desirable to delete the Fc part aft the fusion protein has been expressed and purified.

It is also noted that Ishikawa et al. employed a secretory signal sequence from BST-1 in their Fc fusion construct (page 530, left column). However, such sequences were known to be removed by the host cell (Lo et al. column 5, lines 18-32). Even if this did not occur naturally in the host cell, Lo et al. teach that such sequences are cleaved (column 2, lines 18-37; see also Figure 1). It is also noted that because the secretory signal sequence is appended at the amino terminus prior to the Fc region, it would also be cleaved off upon removal of the Fc region.

The claim limitation of "a protein consisting the amino acid sequence modified by lacking **the last 17 amino acid residues** from a C-terminus in the amino acid sequence of SEQ ID NO:20" is also interpreted to refer to the amino acid sequence SEQ ID NO:20 in which the last 17 residues of this sequence are absent. The Examiner notes that the soluble BST-2/HM1.24-immunoglobulin fusion protein taught by Ishikawa et al. corresponds to the portion of HM1.24 from asparagine 49 to serine 162 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4). Comparing the sequence information in Figure 4 of Ishikawa et al. with instant SEQ ID NO:20, it can be seen that the sequence Asn 49 to Ser 162 corresponds to the amino acid sequence shown in SEQ ID NO:20, but lacking **the last 18 amino acid residues** of SEQ ID NO:20.

As such, the BST-2/HM1.24 fusion protein of Ishikawa also differs in that it lacks the last 18, rather than the last 17 residues, of SEQ ID NO:20.

<u>Figure 4 of Ishikawa:</u>

```
                                             GTGGAATTC   9

ATG GCA TCT ACT TCG TAT GAC TAT TGC AGA GTG CCC ATG  48
Met Ala Ser Thr Ser Tyr Asp Tyr Cys Arg Val Pro Met  13

GAA GAC GGG GAT AAG CGC TGT AAG CTT CTG CTG GGG ATA  87
Glu Asp Gly Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile  26

GGA ATT CTG GTG CTC CTG ATC ATC GTG ATT CTG GGG GTG 126
Gly Ile Leu Val Leu Leu Ile Ile Val Ile Leu Gly Val  39

CCC TTG ATT ATC TTC ACC ATC AAG GCC AAC AGC GAG GCC 165
Pro Leu Ile Ile Phe Thr Ile Lys Ala Asn Ser Glu Ala  52

TGC CGG GAC GGC CTT CGG GCA GTG ATG GAG TGT CGC AAT 204
Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg Asn  65
                                                *
GTC ACC CAT CTC CTG CAA CAA GAG CTG ACC GAG GCC CAG 243
Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln  78

AAG GGC TTT CAG GAT GTG GAG GCC CAG GCC GCC ACC TGC 282
Lys Gly Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys  91

AAC CAC ACT GTG ATG GCC CTA ATG GCT TCC CTG GAT GCA 321
Asn His Thr Val Met Ala Leu Met Ala Ser Leu Asp Ala 104
 *
GAG AAG GCC CAA GGA CAA AAG AAA GTG GAG GAG CTT GAG 360
Glu Lys Ala Gln Gly Gln Lys Lys Val Glu Glu Leu Glu 117

GGA GAG ATC ACT ACA TTA AAC CAT AAG CTT CAG GAC GCG 399
Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln Asp Ala 130

TCT GCA GAG GTG GAG CGA CTG AGA AGA GAA AAC CAG GTC 438
Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val 143

TTA AGC GTG AGA ATC GCG GAC AAG AAG TAC TAC CCC AGC 477
Leu Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser 156

TCC CAG GAC TCC AGC TCC GCT GCG GCG CCC CAG CTG CTG 516
Ser Gln Asp Ser Ser Ser Ala Ala Ala Pro Gln Leu Leu 169

ATT GTG CTG CTG GGC CTC AGC GCT CTG CTG CAG TGAGATC 556
Ile Val Leu Leu Gly Leu Ser Ala Leu Leu Gln ...     180

CCAGGAAGCTGGCACATCTTGGAAGGTCCGTCCTGCTCGGCTTTTCGCTTG 606

AACATTCCCTTGATCTCATCAGTTCTGAGCGGGTCATGGGGCAACACGGTT 657

AGCGGGGAGAGCACGGGGTAGCCGGAGAAGGGCCTCTGGAGCAGGTCTGGA 708

GGGGCCATGGGGCAGTCCTGGGTGTGGGGACACAGTCGGGTTGACCCAGGG 759

CTGTCTCCCTCCAGAGCCTCCCTCCGGACAATGAGTCCCCCCTCTTGTCTC 810

CCACCCTGAGATTGGGCATGGGGTGCGGTGTGGGGGGCATGTGCTGCCTGT 861

TGTTATGGGTTTTTTTTGCGGGGGGGGTTGCTTTTTTCTGGGGTCTTTGAG 912

CTCCAAAAAATAAACACTTCCTTTGAGGGAGAGCAAAAAAAAAAAAAAAAA 963

AAAAAAAAAAAAAAAAAAAGAATTCCACCACA                    996
```

FIG. 4. Nucleotide and predicted amino acid sequence of human BST-2 cDNA. The putative transmembrane region is underlined. Two potential sites of N-linked glycosylation are indicated by asterisks. This sequence data have been deposited with DDBJ/EMBL/GenBank under Accession No. D28137.

<u>SEQ ID NO:20 as disclosed instantly:</u>

```
<210> 20
<211> 132
<212> PRT
<213> Homo sapiens

<220>
<223> Amino acid sequence of soluble HM 1.24 antigenic
      protein

<400> 20
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
  1               5                  10                  15

Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
             20                  25                  30

Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
         35                  40                  45

Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
     50                  55                  60

Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
 65                  70                  75                  80

Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
                 85                  90                  95

Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
            100                 105                 110

Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser
        115                 120                 125

Ala Leu Leu Gln
    130
```

Therefore, Ishikawa et al. disclose a soluble HM1.24 antigen protein having the amino acid sequence modified by lacking 18 amino acid residues from the C-terminus of SEQ ID NO:20, while the instantly claimed invention recites a protein modified by lacking 17 amino acid residues from the C-terminus of SEQ ID NO:20. In other words, the instant claims invoke proteins comprising the sequence from amino acids 49 to 163 of full-length HM1.24, while the soluble HM1.24 antigen protein of Ishikawa et al. ranges from amino acids 49 to 162. The Ishikawa et al. protein is missing an additional residue from the C-terminus, namely the alanine residue at position 163 of the full-length protein.

However, the courts have ruled that in the case where the claimed ranges “overlap or lie inside ranges disclosed by the prior art” a prima facie case of obviousness exists. See MPEP 2144.05.

In the instant case, the teachings of Gastinel et al. and Lauffer et al. establish that deleting amino acids from a transmembrane protein was known to have effects on the physical properties of the protein, namely on the protein’s solubility. Lauffer et al. further contemplate soluble fusion proteins composed of “various portions of the extracellular domains of human membrane proteins” (column 1, lines 46-56). Such teachings indicate that the particular amino acids sequence of a transmembrane receptor was known to be a result-effective variable.

Therefore, it would have been obvious to one of ordinary skill in the art to vary the amino acid sequence of the soluble HM1.24 antigen protein of Ichikawa et al. by including an additional amino acid at the region corresponding to the C-terminus of HM1.24. In particular, because Ishikawa et al. taught that the next amino acid in the endogenous sequence of HM1.24 is alanine 163, it would have been obvious to include this residue in the construct. Put another way, it would have been obvious to remove 17 rather than 18 amino acids from the C-terminus of HM1.24 when preparing the soluble HM1.24 antigen protein.

Furthermore, when taken together with the general knowledge in the art that the amino acid alanine is a small amino acid that possesses no reactive groups on its side chain, one would have had a reasonable expectation of success including alanine 163 in the soluble HM1.24 antigen protein of Ichikawa et al. because the resulting protein lacking 17 rather than 18 amino acids would be reasonably expected to have the same properties.

In addition, one of ordinary skill in the art would have had a reasonable expectation of success in using the modified soluble HM1.24 antigen protein of Ichikawa et al. to detect anti-HM1.24 antibodies according to the antibody-capture assay format of Harlow & Lane based on the teachings of Gastinel et al. that soluble receptors maintained the ability to bind to antibodies. Similarly, Lauffer et al. taught that soluble fusion protein of transmembrane receptors retain their biological activity.

It is also possible to analyze the teachings of Ichikawa et al. in view of those of Harlow & Lane, Gastinel et al., Lauffer et al., Laping et al., and Lo et al. In particular, although Ichikawa et al. do not specifically direct the skilled artisan to employ the soluble HM1.24 antigen protein for the purpose of detecting anti-HM1.24 antibodies, known uses for antigens included using solid-phased antigen for the purpose of detecting cognate antibodies in immunochemical assays, as taught by Harlow & Lane.

Further, it was known to use soluble forms of transmembrane receptors in place of full-length membrane-bound forms for technical reasons, as taught by Gastinel et al., Lauffer et al., Laping et al., and Lo et al. Production of such soluble forms using Fc fusions was known (as taught by Ishikawa et al., Lauffer et al., Laping et al., and Lo et al.), and it was further known to be desirable in some instances to subsequently remove the Fc tag (as taught by Laping et al. and Lo et al.). Finally, although the soluble HM1.24 antigen protein of Ichikawa et al. lacks 18 rather than 17 amino acids from the C-terminus of SEQ ID NO:20, based on the knowledge of the amino acid sequence of HM1.24 as taught by Ichikawa et al. as well as the general knowledge in the art, one would reasonably expect the two proteins to possess the same properties.

With respect to claim 2, Harlow & Lane teaches binding antigens to a solid phase as discussed above. One would have had a reasonable expectation of success in binding the soluble HM1.24 antigen protein to a solid phase because Gastinel et al. taught that soluble receptors could be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

With respect to claim 6, Harlow & Lane teaches immobilization of antigens for the antibody-capture assay on microtiter plates (page 563, second paragraph).

With respect to claim 7, Harlow & Lane teaches using a secondary labeled reagent that will specifically recognize the antibody (i.e., a primary antibody against the antibody). See page 563, first paragraph and page 564. Therefore, when conducting antibody capture assays using soluble HM1.24 antigen protein to detect anti-HM1.24 antibodies as discussed above, it would have been further obvious to employ a labeled reagent that specifically recognized anti-HM1.24 antibodies in order to detect antigen-antibody binding.

With respect to claim 13, Harlow & Lane discuss how all immunoassays rely on labeled reagents for detection (pages 591-592). Suitable labels include radioactive compounds, enzymes, biotin, or fluorochromes (page 591, first paragraph).

14. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al., Gastinel et al., Lauffer et al., Laping et al., and Lo et al. as applied to claim 1 above, and further in view of Frank et al. (U.S. 5,646,115).

The references are as discussed in detail above. Harlow & Lane teaches antibody-capture immunochemical assays in which binding of antibody in a test sample to solid phase antigen is

detected using an antibody specific to the test antibody. However, the references fail to specifically teach using a second antibody in addition to the antibody specific to the test antibody.

Frank et al. teach immunochemical assays in which antigen (saliva proteins) are immobilized on a solid phase and used to capture antibodies in a body fluid test sample (column 34, line 22 to column 35, line 45). The reference teaches that the amount of antibody bound to the solid phase can be determined using one or more layers of secondary antibodies. For example, an untagged secondary antibody can be bound to a serum antibody (in the test sample) and the untagged secondary antibody can then be bound by a tagged tertiary antibody). See column 35, lines 35-45.

Therefore, it would have been further obvious to one of ordinary skill in the art to employ a second antibody (tagged tertiary antibody) as taught Frank et al. in addition to the primary antibody taught by Harlow & Lane in the method of Harlow & Lane, Ishikawa et al., Gastinel et al., Lauffer et al., Laping et al., and Lo et al. in order to achieve the same purpose, namely that of determining the amount of antibody in the test sample that is bound to the solid phase. More particularly, one would be motivated to include an additional antibody layer in this manner in order to determine the amount of anti-HM1.24 antibody in a test sample.

Response to Arguments

15. Applicant's arguments filed 10/14/2009 have been fully considered. Although technically moot in light of the new grounds of rejection set forth above, certain of Applicant’s remarks will be addressed below.

With respect to the rejections of claims 1-2, 6-7, 13, and 17 under § 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al., Gastinel et al., and Lauffer et al., Applicant argues that in Ishikawa, the truncated HM1.24 antigen protein was attached to both a secretory signal sequence at the N-terminus and to an IgG Fc region at the C-terminus. Applicant argues that on the basis of the Ishikawa reference, a person of ordinary skill in the art would consider that the secretory sequence and the IgG Fc are essential for having secretory activity. Applicant contrasts this with the instant invention, in which a secretory sequence and IgG Fc need not be attached. See Reply, pages 15-17.

This is not found persuasive because Applicant is conflating the terms "soluble" and "secretory". Applicant has clarified that the term "soluble," as it is used according to the instant invention, refers to the fact that the protein is <u>not bound to a cell membrane</u> (Reply, page 14, last paragraph). However, Applicant also urges that this term also means a "secretory" protein. However, "soluble" and "secreted" are not one and the same. It is agreed that "soluble" means not bound to a cell membrane. However, at the time of the instant invention, a secreted or secretory protein was defined as one which is transported across or through a membrane when it is expressed in a suitable host cell (see WO 98/37094 at page 2, lines 9-14).

As such, a "soluble" protein is not necessarily a "secretory" protein. For example, cytoplasmic proteins are soluble but are not secretory proteins because they are present inside the cell rather than being secreted outside the cell.

For these reasons, even assuming for the sake of argument that one of ordinary skill in the art would understand the secretory signal sequence and Fc region to be essential for "secretory" activity as argued by Applicant, it does not follow from this that one would

understand these sequences to be essential for *solubility*. Rather, one of ordinary skill in the art would reasonably expect that the truncated HM1.24 antigen protein of Ishikawa et al. would be "soluble" since it lacks the transmembrane domain (Ishikawa et al., page 530, left column) and therefore would not be bound to a cell membrane. Consequently, the evidence of record suggests that the truncated HM1.24 protein would be soluble, regardless of the presence or absence of the secretory signal sequence and Fc region.

Furthermore, even if one would understand the secretory signal sequence and Fc region to be essential for “secretory” activity as argued by Applicant, the prior art recognized the desirability of subsequently removing these heterologous sequences after secretion of the target protein (see discussion of Laping et al. and Lo et al. above). There is nothing in Ishikawa et al. that would teach away from subsequently removing these sequences after the HM1.24 antigen had already been secreted. Rather, the evidence of record suggests that the ordinary artisan would appreciate that these sequences would no longer be needed at this point.

In addition, as discussed above, secretory signal sequences are removed by the host cell prior to secretion. As such, motivation to remove the N-terminal secretory signal sequence is not necessary because the evidence of record indicates that this sequence would already be absent in the secreted HM1.24 antigen protein of Ishikawa et al.

Applicant further argues that Harlow, Gastinel, and Lauffer do not suggest the use of a C-terminal truncation to obtain a secretory type protein. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375

(Fed. Cir. 1986). In the instant case, it is the Ishikawa reference which teaches a C-terminally truncated form of HM1.24.

Conclusion

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Mark L. Shibuya/
Supervisory Patent Examiner, Art Unit 1641